REMARKS

Reconsideration of the above application is respectfully requested. Claims 13-27 are pending in the application. Claims 13-27 have been rejected. Claims 13, 14, 17, 20, and 27 have been amended. Claim 21 has been cancelled.

Claim 13 has been amended to specify that the camptothecin derivative is CPT-11. Support for this amendment is found in the specification at; for example, page 2 lines 3-5, page 3, lines 3-9, as well as original Claims 2 and 6. In addition, claim 13 has been amended to recite that the agents are administered intravenously or orally. Support for this amendment found in the specification at, for example, in Examples 1-5 in the detailed description. Claims 14, 17, 20, 21, and 27 have been amended to remove the redundancy created from newly amended claim 13.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the December 1, 2005 office action.

REJECTION UNDER 35 U.S.C. §103

Claims 13-27 stand rejected as allegedly obvious under 35 U.S.C. § 103 over Furuta et al. (Jpn J. Cancer Chemoth 18(3): 393-402, 1991). Applicants respectfully traverse the rejection under 35 U.S.C. §103 as obvious over Furuta in view of the following remarks.

The Examiner alleges that Furuta et al. discloses "a method of treating a tumor (L1210 Leukemia), comprising administering an effective amount of a camptothecin derivative, as a first agent, in combination with administration of an effective amount of a topoisomerase II inhibitor as a second agent, wherein the agents are administered simultaneously, semi-simultaneously, or separately and wherein the first and second agents provide a synergistic effect." (Dec. 1, 2005 Office Action, page 3, second paragraph). However, applicants note at the outset that Furuta only recites intraperitoneal (i.e., directly via a shunt to the abdominal cavity) administration of a camptothecin derivative in combination with a topoisomerase II inhibitor, to treat leukemia, *a blood*

borne cancer, which is not a tumor. Applicants will further discuss this significant difference below.

Establishment of *prima facie* obviousness requires three conditions. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that the Examiner has not shown where the motivation to establish a *prima facie* case of obvious is found in Furuta. Specifically, the Examiner asserts that the differences between applicants' claimed method and the method taught by Furuta is 1) the type of tumor that is treated, 2) the form of administration, and 3) notes that Furuta is silent on optimum dose.

Applicants claimed invention is directed to a method of treating a solid tumor, comprising administering CPT-11 in combination with topoisomerase II inhibitor, wherein the agents are administered intravenously or orally, and the combination provides a therapeutic synergy superior to each of the agents used alone at its optimum dose. (emphasis added).

I. NO MOTIVATION, TEACHING, OR SUGGESTION EXITS TO TREAT SOLID TUMORS.

First, there is no motivation or suggestion in Furuta to use the claimed combination of agents to treat solid tumors. It is the Examiner's burden to show where in the cited reference it is suggested that the instant combination would be useful to treat solid tumors and applicants respectfully invite the Examiner to point out specifically where the alleged suggestion exists.

In the instant case, Furuta lacks any teaching, suggestion, or motivation to apply the instant combination to solid tumors. At the time applicants' invention was made, a

skilled artisan had no interest in applying the claimed method of treatment in Furuta to solid tumors. More specifically, in the past 10 years since Furuta published, there has been no additional literature for the use of this combination for the treatment of solid tumors until Applicants filed the instant application. In the past decade there has not been the slightest hint of motivation to use camptothecin in combination with a topoisomerase II inhibitor for treating solid tumors. Based on this evidence, the knowledge generally available at the time of Applicants' invention demonstrates that this claimed method of use was not recognized by those skilled in the art. The lack of motivation to pursue this combination in solid tumors is apparent on the facts. Now, 10 years later, in a completely different form of cancer, Applicants have claimed a method of treating solid tumors with two agents to result in therapeutic synergy. This claimed method is not taught or suggested by Furuta. The lack of any development or use of, let alone any example, related to the current claims over the past 10 years, illustrates on its face, the non-obviousness of the pending application over the Furuta reference.

Additionally, the Examiner contends that topoisomerase II inhibitors are known in the art to treat solid tumors, citing Felix et al. and Kushner et al. (Dec. 1, 2005 office action, lines 18-22) and concludes that is it obvious to apply Furuta's method to solid tumors. However, Applicants respectfully submit these references do not teach that topoisomerase II inhibitors are useful to treat solid tumors and invite the Examiner to specifically reference (i.e., page and line number) where in these references it is allegedly taught. Both references relate to the danger of leukemia as a result of using a topoisomerase II inhibitor to treat solid tumors. Neither reference explicitly nor implicitly suggests that the use of a topoisomerase II inhibitor to treat solid tumors is a good idea. In fact, upon reading the references in their entirety, it appears one skilled in the art would be motivated to avoid using a topoisomerase II inhibitor to treat solid tumors because of the recited risk of leukemia. These references thus teach away from the claimed invention. Further, as far as Applicants can tell, both these references cited by the Examiner have no information from an efficacy perspective, as to suggest that topoisomerase II inhibitors are useful for the treatment of solid tumors. Hence, Applicants respectfully submit that the Examiner has failed to show that the prior art teaches that topoisomerase II inhibitors are useful for the treatment of solid tumors.

II. DIFFERENCES BETWEEN LEUKEMIA AND SOLID TUMORS AND DIFFERENCES BETWEEN ROUTES OF ADMINISTRATION CREATE A LACK OF A REASONABLE EXPECTIONATION OF SUCCESS.

Applicants respectfully submit that the Examiner has not shown that the person skilled in the art of treating leukemia at the time of the present invention would have a reasonable expectation that the same combination would be successful in treating solid tumors. "Tumor," is defined as "an abnormal benign or malignant growth of tissue that possesses no physiological function and arises from uncontrolled usually rapid cellular proliferation." (emphasis added)(Merriam-Webster On-Line)(see Exhibit A). Leukemia, however, is a *blood-borne* disease, characterized by "an abnormal increase in the number of white blood cells in the tissues and often in the blood." (Merriam-Webster On-Line) (see Exhibit B). Furthermore, the Merck Manual of Medical Information divides malignancies into two distinct groups: those of the blood and blood-forming tissues (leukemias and lymphomas) and solid tumors. (see Merck Manual of Medical Information, 2nd ed., online version)(see Exhibit C). Yet, the Examiner states (Office Action 12/01/2005, page 3, line 5):

"Furuta el al. discloses a method of treating a tumor…"

Hence, applicants respectfully submit that the Examiner's characterization of leukemia as a tumor is incorrect. Further, it is widely recognized in the art that a treatment regiment which is successful against blood-borne cancer (i.e., leukemia) will not necessarily be successful against solid tumors. This is in part due to inherent differences between solid tumors and leukemia. Leukemia is a blood-borne cancer, ubiquitous throughout the entire body, whereas solid tumors are typically localized. Further, as chemotherapy affects cell division, cancers with high growth fractions (i.e., leukemia) are more sensitive to chemotherapy than solid tumors because as a larger proportion of the targeted cells are undergoing cell division at a given time. Hence, chemotherapy is generally more effective in leukemia than solid tumors because near the center of some solid tumors, cell division has effectively ceased, making them insensitive to chemotherapy. Another distinction between solid tumors and leukemia is the fact that chemotherapeutic agents often do not reach the core of a solid tumor.

Based on the remarks above, it is clear that leukemia is not a tumor and that leukemia and solid tumors are very different diseases. Hence, applicants respectfully submit that one skilled in the art could not predict, with any reasonable expectation of success, that just because a therapy may be useful against leukemia, that it would be successful against solid tumors as well. Thus, one skilled in the art would not reasonably expect that combining CPT-11 with a topoisomerase II inhibitor would be useful to treat solid tumors because of the unpredictable nature of applying a known treatment for leukemia to solid tumors. It is the Examiner's burden to show why one skilled in the art would have such an expectation of success in treating solid tumors with a known leukemia treatment and applicants respectfully submit this burden has not been met.

The Furuta reference is also solely limited to administration of the active agents intraperitoneally (i.e., via abdominal cavity). However, the currently amended claims are limited to oral and intravenous administration. It is well known in the art that the route of administration may have a large effect in treating cancer and that one skilled in the art cannot, with any reasonable expectation of success, know that just because one form of administration is successful (i.e., intraperitoneal), that another form of administration will also be successful (i.e., oral or intravenous). There are simply too many variables to consider, such as how the digestive tract will interact with the active agent, or in the case of intravenous administration, how a direct administration of an agent into the circulatory system will affect the organs, or whether there will be any blood-brain barrier permeability issues. When intraperitoneal administration is performed, there is no need to consider GI consequences, and the rate of absorption is slower and more localized than when performed intravenously. It is these kinds of factors and considerations that require extensive experimentation, as exemplified in the instant specification, to arrive at the claimed invention. It is the Examiner's burden to show why using different forms of administration in cancer therapy is an obvious variant and applicants respectfully note that the Examiner has failed to give any reason.

Based on the arguments and submissions presented above regarding the non-obviousness of treating different types of tumors and using different forms of administration, applicants respectfully submit that the requirements for *prima facie*

obviousness have not been satisfied, applicants respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

Applicants respectfully submit that the prior art does not teach or suggest all the claims limitations of the instant application as required for a *prima facie* case of obviousness. Furuta, the only prior art cited by the Examiner under 35 U.S.C. § 103, does not teach the 1) type of tumor, 2) dosing, 3) therapeutic synergy, or 4) form of administration, that are recited by pending claim 1.

Applicants respectfully submit that the Examiner's allegations have failed to satisfy all of these conditions for a *prima facie* case of obviousness. Any failure alone would suffice to show that the *prima facie* case has not been established. In light of the fact that the *prima facie* case for obviousness has not been established, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

III. UNEXPECTED RESULTS SHOW NONOBVIOUSESS

Assuming arguendo that the claimed subject matter is *prima facie* obvious based on the cited prior art as suggested by the Examiner, applicants submit that the claimed combination has unexpected or surprising effects which could not have been expected by a person of ordinary skill in the art.

The instant combination must be considered to be non-obvious because of the unexpected or surprising nature of the claimed combination's activity to treat solid tumors. Evidence of this unexpected or surprising effect is set forth in the specification which provides that the claimed combination is more active at a lower dose than the highest non-toxic dose of each single agent for the treatment of solid tumors. To the contrary, the Examiner asserts that one of ordinary skill in the art would have been motivated to use the method embraced by the reference to formulate the method currently claimed with the expectation of obtaining therapeutic synergy when using a combination of camptothecin and a topoisomerase II inhibitor to treat solid tumors.

The Examiner states that synergism or therapeutic synergy is not limited to an optimum dose and therefore Furuta does not have to disclose an optimum dose in reporting synergism. (Office Action, Dec. 1, 2005; page 6, lines 5-7). However, applicants respectfully note that an "applicant is entitled to be his or her own

lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s)." *In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994) (inventor may define specific terms used to describe invention, but must do so "with reasonable clarity, deliberateness, and precision" and, if done, must "'set out his uncommon definition in some manner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change" in meaning). Further, where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings"). Accordingly, applicants respectfully point the Examiner to page 5, paragraph 3, where therapeutic synergy of a combination is defined to occur when said combination is "therapeutically superior to one or other of the constituents uses at its optimum dose."

In view of the remarks above, applicants respectfully submit that the Examiner is required to examine the instant claims in light of applicants' own definition of therapeutic synergy. Therefore, the data from Table 3 in Furuta does not fall within the scope of applicants claim, as the Examiner alleges, because Furuta does not disclose optimum dose. Applicants submit it is improper for the Examiner to infer from Furuta's silence with respect to optimum dose, that such a limitation exists in Furuta. However, applicants' current claims make explicit reference to optimum dose. Applicants respectfully submit it is improper for the Examiner to imply this characteristic in Furuta from mere silence. It is clear that optimum dose is not taught or suggested by Furuta.

The Examiner also concludes that in the absence of a side-by-side comparison, one cannot assume that the composition in Furuta would not give the same results. Applicants respectfully note however that it is the Examiner's burden to show that the cited prior art reference would give the same results as applicants' application. In the absence of such, applicants respectfully submit that the Examiner must accept applicants' data at face value.

Applicants also respectfully submit that the data in the specification is evidence of unexpected results because the synergism recited in Furuta is solely limited to the context of treating leukemia. As discussed above, leukemia and solid tumors are very different diseases. Therefore, just as one skilled in the art cannot reasonably expect that a given treatment for leukemia will be effective in treating solid tumors, so too can one skilled in the art not reasonably expect synergistic results in treating solid tumors simply because the same combination is seen to have synergism when treating leukemia. Thus, one skilled in the art would not reasonably expect synergistic results when treating solid tumors with combination of CPT-11 and a topoisomerase II inhibitor.

In view of the remarks above, applicants respectfully submit that the Examiner has failed to meet their burden, and therefore applicants' respectfully submit the data provided in the specification rebuts any alleged *prima facie* case of obviousness.

Based on the above arguments and the amendments made herein, applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider the rejections set forth in the December 1, 2005 Office Action and earnestly solicit allowance of the claims pending in the subject application. Applicants' undersigned attorney may be reached at the phone number listed below if the Examiner believes that this will help advance prosecution and allowance of the subject application.

Respectfully submitted,

Date: Nov. 8, 2006

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